INFLUENCE OF FAT SUPPLY ON ELECTROLYTE MOVEMENT

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by

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I. INTRODUCTION

The fat emulsion prepared in our laboratory for intravenous infusion has been found to possess several nutritional advantages. TSUKADA[1], OSA[2], KUYAMA[3] and HANAFUSA[4] have already reported its protein sparing action and MATSUDA[5] its glycogen sparing action. TAMAKI[6] showed that the infusion of fat emulsion before and after operation is very effective in maintaining fluid distribution at near normal levels. This action was further confirmed by KOBAYASHI's[7] experimental studies. Changes in fluid distribution often accompany electrolyte disturbances. Since the organism strives to maintain life by preserving its "milieu interieur" by keeping electrolyte concentration and fluid volume at a certain level, it was hypothesized that intravenous injections of fat emulsion might help to restore electrolyte distribution in patients with many different kinds of pathological conditions. In addition, it must be kept in mind that this fat emulsion made from sesame oil contains many essential fatty acids (EFA), which may play an important role as constant element. Referring the relation of fat supply and water and electrolyte metabolism especially, it is necessary to investigate the influence of fat supply on electrolyte movement from the following point of view at the same time. Since EFA are believed to have a close connection with cholesterol-metabolism and an important role in the synthesis of corticosteroids (NAGASE[8], MATSUDA[5], TAMAKI[21] and SINCLAIR[9]), the influence of this fat emulsion on water and electrolyte metabolism is quite complex.

This experiment was performed in an attempt to (a) clarify the relationship between synthesis of mineralocorticoids and EFA by determining urinary electrolyte, (b) study the relationship between electrolyte movement and fat supply by the use of fat emulsion and insult, i. e. surgery.

II. EXPERIMENTAL ANIMALS AND METHOD

A. Experimental Animals

The animals used were adult male dogs weighing approximately 10 kg and male albino rats of the Wistar strain supplied by Animal Center of Kyoto University. A low fat diet (Table 1) was given to the dogs for 10 days to 8 weeks before the experiment, and only those that kept a steady weight and appetite and had no

diarrhea or wound infection were chosen for the test. The rats were divided into two groups; one was fed a fat-free diet and the other a fat diet (Table 2) plus water for more than 8 weeks.

B. Fat Emulsion

For one week before gastrectomy and 10 days after, 2cc per kg (0.4g as fat) of the 20% sesame oil emulsion prepared in our laboratory, or 4 to 6cc per kg (0.8 to 1.2g as fat) mixed with 10cc of 5% glucose per kg, 10cc of RINGER's solution per kg, Vit. B_1, B_2, B_5 and C were infused intravenously in dogs every day.

C. Measurement of Sodium and Potassium Concentrations

Sodium and potassium concentrations were determined by BECKMANN's Flame Spectrophotometer and LANGE's Flamephotometer[10)~17)].

1. Sodium and Potassium Concentrations in Serum and Whole Blood

Table. 1
Low fat diet for a dog weighing 10 kg

	Amount	Cal.	Fat	Protein
Rice	150 g	510 Cal	2.7 g	14.6 g
Dry fish	20	49	0.7	10.8
Brewers yeast	1	3	—	—
Water	400cc	—	—	—
Total	—	562	3.4	25.4

Table. 2
Fat-free diet and fat diet for rats

	Fat-free diet	Fat diet
Starch	80%	64%
Casein	16	12.8
Salt mixture*	3	2.4
Vit. mixture	0.5	0.4
Choline·HCl	0.5	0.4
Sesame oil	—	20
Calorie/g	ca 4 Cal	ca 5 Cal

*Composition of salt mixture

NaCl	17.3g	Cal. lact.	139.0
NaH_2PO_4	34.7	$MgSO_4$	26.6
K_2HPO_4	95.4	KJ	10.0
$CaH_4(PO_4)_2H_2O$	51.0		

In order to measure the serum concentration, 6 bottles of standards ranging from K 1.25 meq./l and Na 35meq./l to K 7.50 meq./l and Na 175 meq./l were prepared. Then the serum and the standard solution were severally diluted 50 times for measurement. In an attempt to determine the concentration in whole blood, 6 bottles of standard solution were prepared ranging from K 15 meq./l and Na 15 meq./l to K 90 meq./l and Na 90 meq./l. Then the whole blood and the standard solution were diluted 100 times for measurement. The sodium and potassium concentrations in the blood corpuscles were calculated by the following formula, the hematocrit value being measured at the same time.

$$B = C \cdot Ht + (1 - Ht) \cdot S \quad \therefore \quad C = \frac{B - S}{Ht} + S$$

B : Concentration in Whole Blood
C : Concentration in Blood Corpuscles
S : Concentration in Serum
Ht : Hematocrit Value

2. Sodium and Potassium Concentrations in Urine

From two different kinds of original solution; (Na 60 meq./l, K 20 meq./l, Urea 20 g/l and Na 10 meq./l, K 20 meq./l, Urea 20g/l) a series of 14 standard solutions of Na (from 2.5 meq./l to 240 meq./l) and 9 of K (from 5 meq./l to 80 meq./l) was prepared. Then each of them and the urine were diluted 50 times.

3. Sodium and Potassium Content of Foods (Table 3)

Measured quantity of foods (rice, barley, dry fish, brewers yeast, skim-milk and flour) were calcinated moistly[18] and measured. Rice, barley, dry fish and brewers yeast were given to the experimental dogs as a standard diet before and after operation, and skim-milk and flour were added as necessary.

Table. 3 Sodium and potassium content and calories in 100g of food

	Potassium	Sodium	Calories
Rice	1.5 meq.	0.5 meq.	340 Cal
Barley	4.1	0.7	353
Dry fish	16.0~17.4	32.0~43.3	246
Brewers yeast	27.7	7.7	324
Sugar	—	—	396
Skim-milk	34.5	16.2	359
Flour	2.3	1.3	364

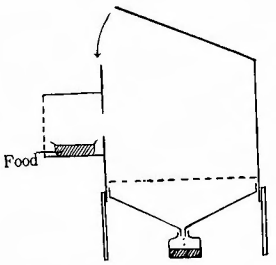


Fig. 1 Feeding box for dog

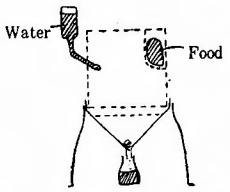


Fig. 2 Feeding box for rat

D. Method of Collecting Urine

Dogs fed this low fat diet were placed in feeding boxes as shown in Fig. 1. After he got used to living there for 2 or 3 days, the experiment was begun. The floor of this feeding box was of wire netting so that the dog's faeces remained on it and urine was accumulated in a bottle through a funnel beneath. The dog lived in the box during the period of the experiment and took food from a side box. The urine was all collected, together with catheterized residual in the bladder, every 24 hours and measured. Each of the rats was fed separately in its own feeding box as shown in Fig. 2. This feeding box had one filter and double bottoms made of wire mesh to prevent food and faeces from contaminating the urine. It helped in collecting the urine to cover the funnel with liquid paraffin, but the volume was so little that the wire mesh and funnel were rinsed off with 5 to 10cc of purified water to collect all the urine.

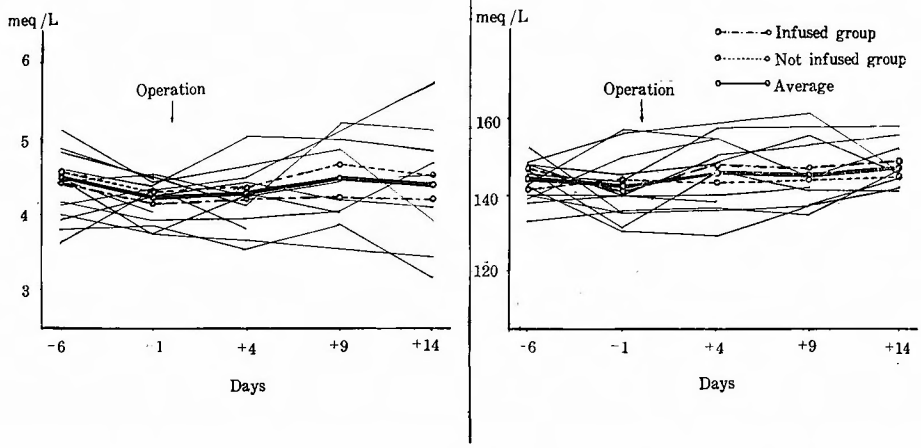
Ⅲ. RESULTS

A. The Serum Electrolyte Concentration and Electrolyte Balance of Dogs, before and after Gastrectomy, Treated with Repeated Infusions of Fat Emulsion

1. Sodium and Potassium Concentration in Serum

The serum potassium concentration of normal dogs on the standard diet was 3.61 to 5.13 meq./*l* before experiment (average 4.49 meq./*l*). The sodium concentration was 133.0 to 152.8 meq./*l* (average 144.6 meq./*l*). These value are similar to those of healthy humans (K 4.65 meq./*l*, Na 143.0 meq./*l*) (HINOHARA[19]). Fig. 3 shows the blood levels on the 6th and lst days before operation, and on the 4th, 9th and 14th postoperative days. Sodium and potassium tended to go decrease with fluid infusions before operation and to increase slightly after operation, but they were never far from the normal range. It was hard to recognize significant differ-

Fig. 3 Potassium concentration in serum Sodium concentration in serum



ences between the average concentrations of the fat-emulsion-infused group 8 and the control group 6.

2. Electrolyte Balance

a. In Cases Receiving Repeated Small Infusions of Fat Emulsion

i. Low Potassium Diet

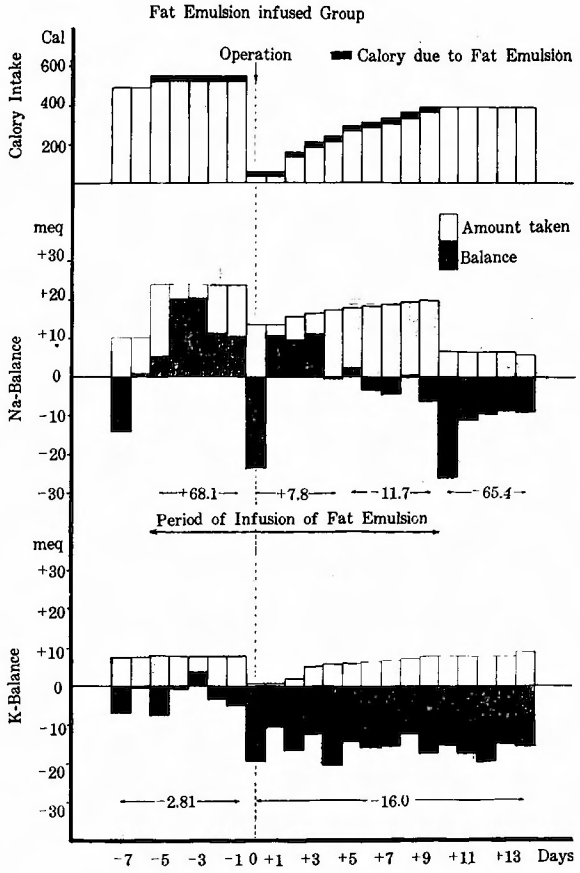
Table. 4 Low potassium diet and fluid infusion before and after gastrectomy for a dog weighing 10kg

Days	Rice	Dry fish	Brewers yeast	Water	5% Glucose	Ringer's sol.	Vitamins	Cal.	Fat* emulsion
−7～−6	150g	20g	1 g	400cc	—	—	—	562 Cal.	—
−5～−1	150	20	1	100	100cc	100cc	B_1 5mg, B_2 5, B_6 5, C 50	582	20cc
0	—	—	—	—	100	100	〃	20	20
+1	—	—	—	—	100	100	〃	20	20
+2	100×1/7	15×1/7	1	400	100	100	〃	77	20
+3	100×2/7	15×2/7	1	400	100	100	〃	131	20
+4	100×3/7	15×3/7	1	400	100	100	〃	186	20
+5	100×4/7	15×4/7	1	400	100	100	〃	238	20
+6	100×5/7	15×5/7	1	400	100	100	〃	292	20
+7	100×6/7	15×6/7	1	400	100	100	〃	346	20
+8～+9	100	15	1	400	100	100	〃	400	20
+10～+14	100	15	1	400	—	—	—	380	—

(*In Fat Emulsion Infused Group only)

The diet is described in Table 4; animals received 55 to 60 Cal/kg/day before gastrectomy, fluid infusions only for 2 days after, and then gradually up to 35 to 40 Cal/kg/day by the 8th day after operation. No supplementary oral potassium

Fig. 4 — 1 Low Potassium Diet



was added. 2cc per kg of 20% sesame oil emulsion was infused in the experimental group every day. For 3 weeks, from 7 days before operation until 14 days after, intake and urinary output of potassium and sodium were measured daily, and balance calculated (Fig. 4). The potassium balance was slightly negative before operation, and became even more so after, and stayed negative even when protein anabolism would have been expected one week later. The fat-emulsion-infused group lost an average of 16.0 meq. and the control group 17.1 meq. of potassium per day. Sodium balance suddenly became positive when fluid infusion was begun before operation and remained so up until one day before operation. It was negative for 24 hours after operation and then became positive. On the 5th day it suddenly became negative again. The fat-emulsion-infused group had more sodium retention before operation and the control group more sodium retention and excretion after operation. The fat-emulsion-infused group had a greater negative sodium balance for 24 hours after operation. Both groups lost weight after operation steadily for

over one week. The fat-emulsion-infused group lost a little less weight than the control group.

Fig. 4—2 Low Potassium Diet

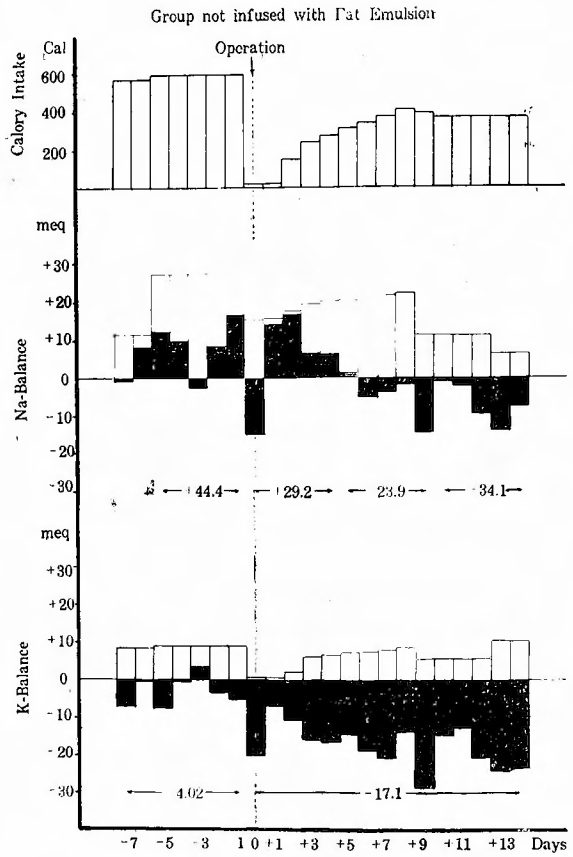


Table. 5 High potassium diet and fluid infusion before and after gastrectomy for a dog weighing 10kg

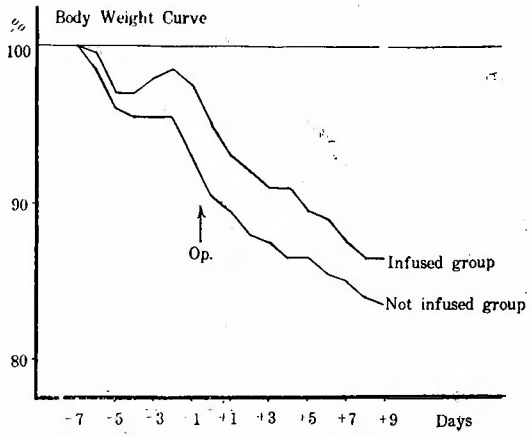
Days	Rice	Dry fish	Brewers yeast	Water	K	5% Glucose	Ringer's sol.	Vitamins	Cal.	Fat* emulsion
−7〜−6	170g	40 g	1 g	400cc	10meq.		−		679Cal.	
−5〜−1	170	40	1	400	10	100cc	100cc	B1 5mg B2 5 B6 5 C 50	699	20cc
0	−	−	−	−	−	100	100	〃	20	20
+ 1	−	−	−	−	−	100	100	〃	20	20
+ 2	170×1/5	40×1/5	1	400	20	100	100	〃	158	20
+ 3	170×2/5	40×2/5	1	400	20	100	100	〃	293	20
+ 4	170×3/5	40×3/5	1	400	20	100	100	〃	428	20
+ 5	170×4/5	40×4/5	1	400	20	100	100	〃	563	20
+ 6〜+ 9	170	40	1	400	20	100	100	〃	699	20
+10〜+14	170	40	1	400	20	−	−	−	679	−

(*In Fat Emulsion Infused Group only)

ii. High Potassium Diet

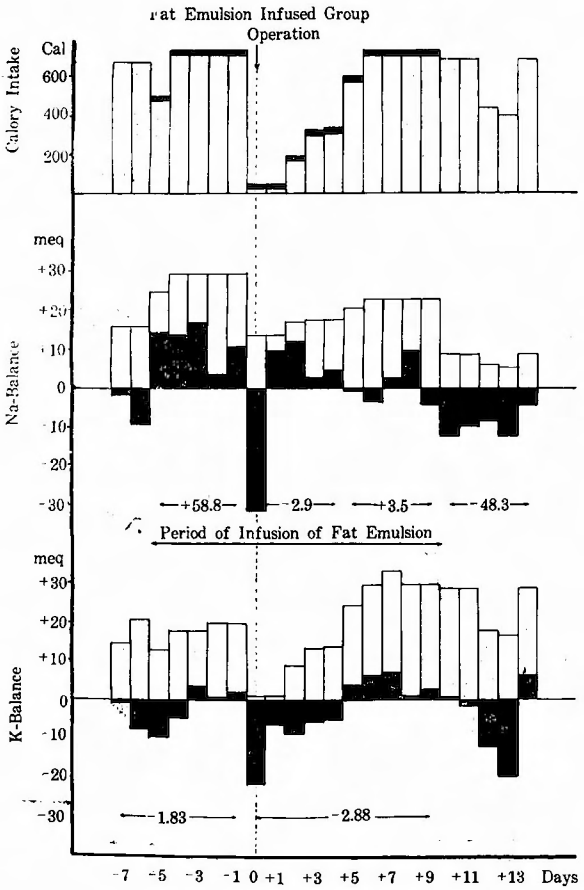
The results of the preceding experiment indicated that the calorie and potassium intake were low, so potassium as phosphate (K_2HPO_4 and KH_2PO_4 in a ratio of 2 : 0.4)[20] was added to the diet. The quantity added was 1 meq./kg before operation and 2 meq./kg after. The calorie intake after the operation was increased sooner, and the whole quantity (from 65 to 70 Cal) was supplied on the 6th postoperative day (Table 5 and Fig. 5).

Fig. 4 — 3 Low Potassium Diet



As for the potassium balance, the daily average in both groups before operation, was less negative than in animals on a low potassium diet. It was most negative on the day of operation, then began to increase and became positive on the 5th

Fig. 5 — 1 High Potassium Diet



day after operation. The fat-emulsion-infused group lost less potassium than the control group in the postoperative stage. The daily average loss in the former 9 days after operation was 2.88 meq., and in the latter 6.51 meq., This represented a large difference from Experiment (i).

The sodium balance changed about the same amount as in the preceding test, but the fat-emulsion-infused group lost more sodium in the first 24 hours after operation; therefore there was a total sum loss of sodium in this phase. Moreover, the sodium diuresis of the postoperative stage began somewhat later than in Experiment (i). Through the whole period after the operation, the sodium balance did not seem to be either more positive or more negative than in Experiment (i). The weight curve of the two groups was very different.

b. In Cases Receiving Repeated Infusions of a Large Quantity of Fat Emulsion

A large quantity of fat emulsion was infused every day before and after operation as Table 6 shows. The potassium balance was much more favorable than in the fat-emulsion-infused group of Experiment (a, ii) (Fig. 6). The potassium loss in the first 24 hours after operation was less (28 meq.) and a positive balance was reached as earlier as the 3rd day. The daily average potassium balance was +1.38 meq. from the lst to the 9th day after operation. The changes in sodium balance of each stage became smaller than those of

Fig. 5—2 High Potassium Diet

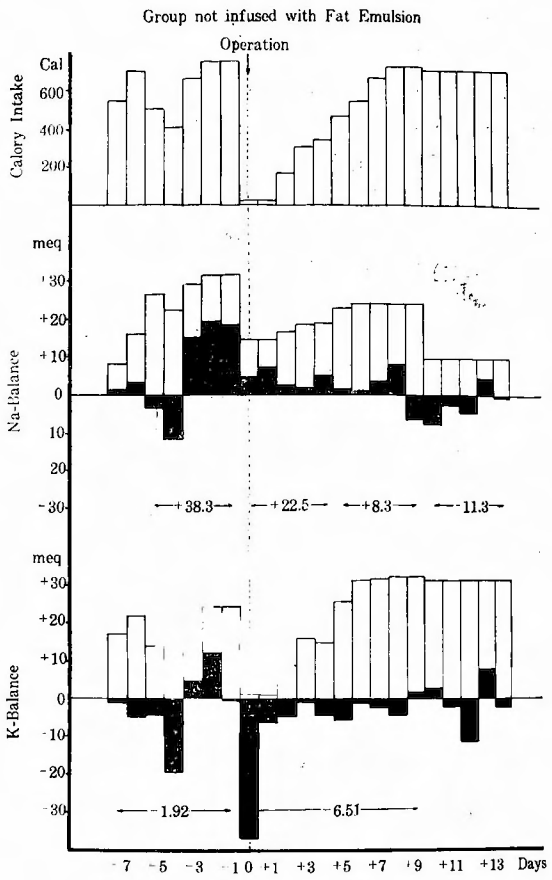


Fig. 5—3 High Potassium Diet

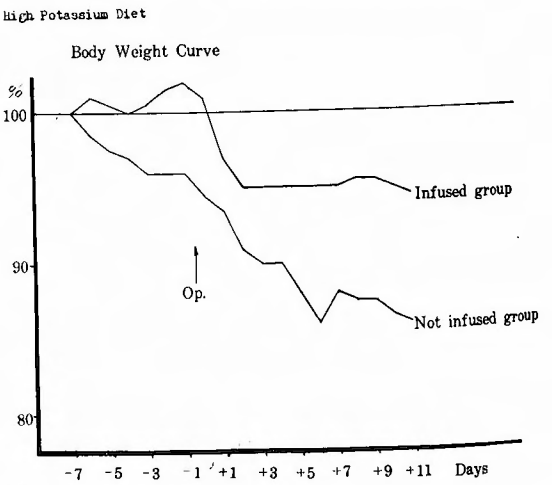


Table. 6 Fluid infusion and repeated infusions of a large amount of fat emulsion

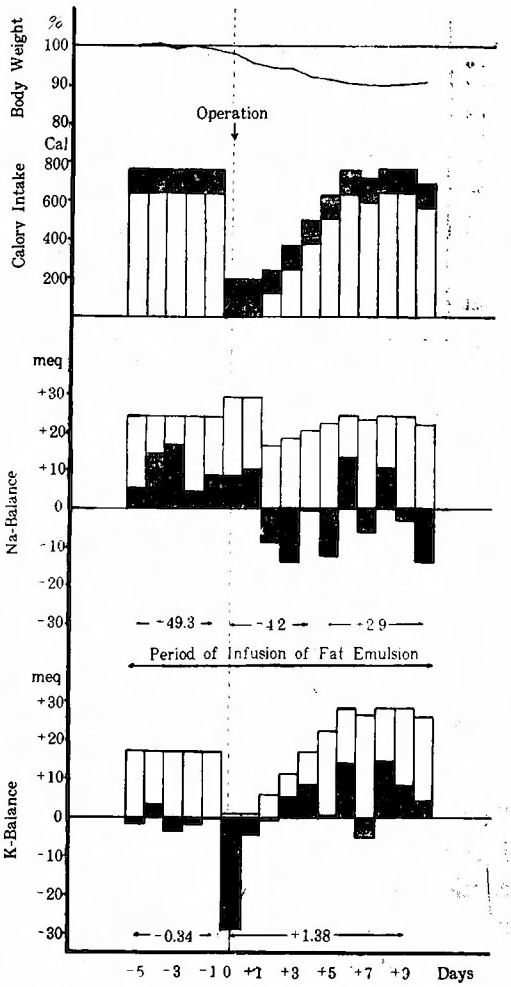
Day	5% Glucose	Ringer's sol.	Fat emulsion
−7～−1	100cc	100cc	50cc
0～+1	200	200	75
+2～+9	100	100	50

Experiment (a, ii), although no clear distinction was made between the sodium retaining stage and the sodium excreting stage after that.

B. Changes in Na/K Ratio in the Urine under Stress

Rats weighing about 200g lived in the feeding box for 7 to 10 days before the experiment. They had been fed ad lib. to maintain constant weight, as shown in Table 2, for 60 to 90 days. Table 7 indicates the diet intake, caloric intake, daily urine volume, daily average electrolyte excretion and the Na/K ratio under non-stress conditions. The fat-free diet group ate more in total weight, but the both groups had about the same caloric intake. The electrolyte intake was 50% higher in the fat-free diet group, but the Na/K ratio of the two diets was the same (0.537). Rats on the fat-free diet excreted more urine than did the fat diet group; 8.8 cc to 12.0 cc (average 10.9 cc) and 1.86 cc to 3.90cc (average 3.02cc), respectively. The fat-free diet group also excreted more sodium and potassium with a somewhat higher Na/K ratio.

Fig. 6 Repeated Injections of a Large Quantity of Fat Emulsion



1. Effect of 1mg Injections of ACTH-Z (Fig. 7 and Table 8)

1mg of ACTH-Z (N. V. Organon-Oss., Holland) was injected into the peritoneal cavity of the rats. After 24 hours, the Na/K ratio of the urine rose to about the same value and then gradually fell, with no difference between the two groups.

Table 7 Dietary intake and urinary excretion of fat diet group and fat-free diet group

	Diet per day	Cal.	Urine volume per day	K Excret. per day	Na Excret. per day	Na/K ratio
Fat diet group	15.5g	77.7 Cal.	3.02cc	0.296meq.	0.180meq.	0.608
Fat-free diet group	18.6	74.3	10.9	0.808	0.580	0.717

(mean of 5 rats in each group for 6 days)

Fig. 7 Alterations of Na/K ratio in urine of rats injected with 1mg of ACTH-Z

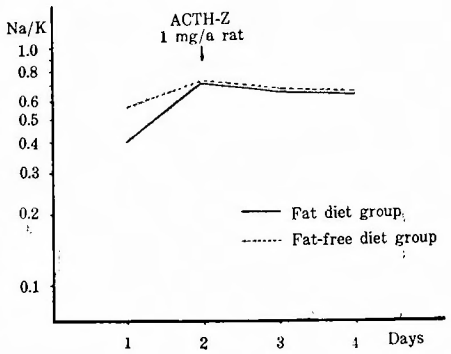


Fig. 8 Alterations of Na/K ratio in urine of rats injected with 4mg of ACTH-Z twice

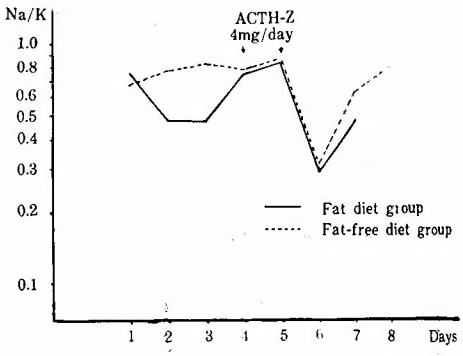


Table 8 Alterations of potassium and sodium in urine of rats injected with 1mg of ACTH-Z

	Fat diet group				Fat-free diet group		
Days	Urine volume	Potassium excretion	Sodium excretion		Urine volume	Potassium excretion	Sodium excretion
1	2.4cc	0.470 meq.	0.188 meq.		11.5cc	0.560meq.	0.312meq.
2	3.6	0.638	0.452		11.4	0.672	0.482
3	2.0	0.420	0.266	ACTH-Z 1 mg	11.2	0.704	0.460
4	2.8	0.368	0.230		10.5	0.760	0.488

(mean of 5 rats in each group)

The Na/K ratio increase was due not to a decreased potassium excretion but to an increase in the sodium excretion. TAMAKI[21] had measured the formaldehydogenic corticosteroid excretion under the same conditions, and reported that there was almost no difference between the two groups, even though the excretion of it in the two groups loaded with that much ACTH generally increased.

Table 9 Alterations of potassium and sodium in urine of rats injected with 4mg of ACTH-Z twice

	Fat diet group				Fat-free diet group		
Days	Urine volume	Potassium excretion	Sodium excretion		Urine volume	Potassium excretion	Sodium excretion
1	8.7cc	0.502meq.	0.373meq.		9.9 cc	0.749meq.	0.500meq.
2	8.0	0.565	0.262		–	1.250	0.936
3	3.9	0.324	0.151		11.7	0.622	0.516
4	5.9	0.524	0.384	ACTH-Z 4mg	16.6	0.912	0.710
5	3.7	0.410	0.354	ACTH-Z 4mg	9.3	0.700	0.618
6	3.1	0.382	0.111		11.9	0.841	0.268
7	1.5	0.417	0.200		11.3	0.995	0.641
8	1.7	0.403	–		8.3	0.805	0.649

(mean of 5 rats in each group)

2. Effect of Two 4mg Injections of ACTH-Z (Fig. 8 and Table 9)

Intraperitoneal injection of 4mg/day of ACTH-Z on two consecutive days caused the Na/K ratio in the urine to rise higher than in the previous experiment. This also was due to increased sodium excretion. However, it fell rapidly to a lower value than in the last test immediately after the second injection and returned more nearly to normal. This fall was caused by a decrease in the sodium excretion. There was no difference between the two groups. This dose was equivalent to about 30 times that ordinarily used clinically, so it was considered sufficient to activate adrenocortical function in rats. TAMAKI had also measured the formaldehydogenic corticosteroid excretion under these same conditions, and it was made clear already with a single injection of ACTH-Z that the formaldehydogenic corticosteroid excretion of the fat diet group increased much more than that of the fat-free diet group, and that the adrenocortical function was certainly activated with much ACTH-Z load. Moreover, there was a distinct difference between the reaction patterns of the two groups.

3. Effect of 3 Days of Fasting (Fig. 9 and Table 10)

Fig. 9 Alterations of Na/K ratio in urine of rats fasting for 3 days

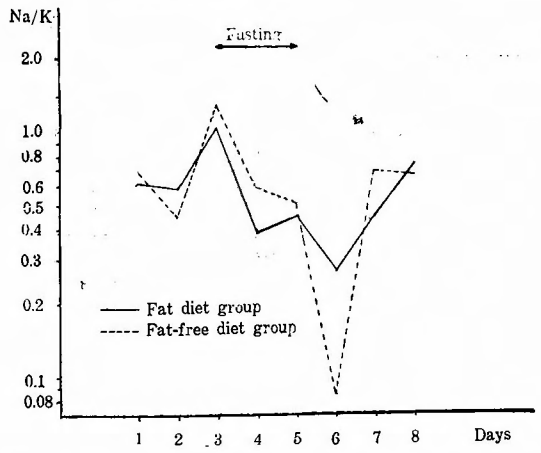


Table 10 Alterations of potassium and sodium in urine of rats fasting for 3 days

Days	Fat diet group				Fat-free diet group		
	Urine volume	Potassium excretion	Sodium excretion		Urine volume	Potassium excretion	Sodium excretion
1	2.5 cc	0.213meq.	0.130meq.		11.2 cc	0.761meq.	0.688meq.
2	6.9	0.203	0.115		14.3	0.867	0.452
3	6.7	0.249	0.255	Fasting	10.7	0.374	1.281
4	7.7	0.432	0.172	Fasting	13.7	0.466	0.593
5	5.7	0.268	0.122	Fasting	4.7	0.244	0.504
6	6.3	0.226	0.061		9.7	0.525	0.084
7	7.5	0.425	0.192		10.3	0.507	0.682
8	8.7	0.502	0.372		9.9	0.749	0.667

(mean of 5 rats in each group)

The standard diet was given after 3 days' fasting with only water allowed. The Na/K ratio rose on the lst day of fasting due to increased sodium excretion, but returned to normal or lower on the 2nd and 3rd days, fell still lower on the day eating was resumed, and then returned to normal. This fall in the Na/K ratio after fasting had ceased was considered to be due to a definite decrease in sodium excretion in both groups.

4. Effect of a Low Sodium Diet for 4 Days (Fig. 10, Table 11 and Table 12)

The sodium content of the two diets was lowered for 4 days and then returned to normal. A conspicuous fall in the Na/K ratio occurred during those 4 days and on the first day that the standard diet was given. This was due to increased potassium excretion and decreased sodium excretion. No difference was noted between the two groups.

Fig. 10 Alterations of Na/K ratio in urine of rats on a low sodium diet for 4 days

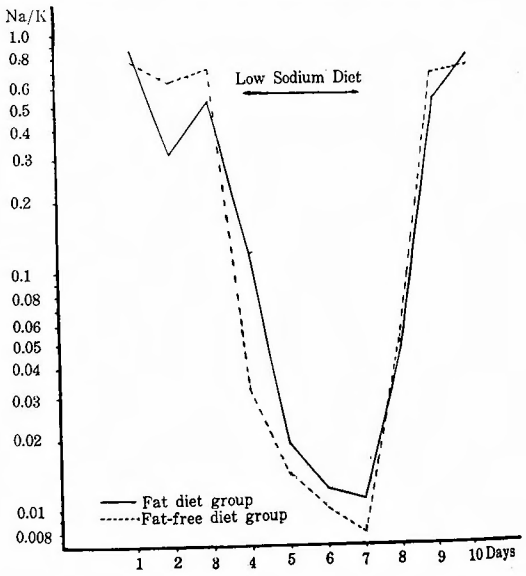


Table 11 Weight composition of salt mixture for low sodium diet

KCl	22.0 g
K_2HPO_4	95.4
$CaH_4(PO_4)_2H_2O$	54.0
Cal. lact.	139.0
$MgSO_4$	26.6
KJ	10.0

Table 12 Alterations of potassium and sodium in urine of rats on a low sodium diet for 4 days

Days	Fat diet group				Fat-free diet group		
	Urine volume	Potassium excretion	Sodium excretion		Urine volume	Potassium excretion	Sodium excretion
1	3.6 cc	0.326meq.	0.280meq.		13.7 cc	0.716meq.	0.552meq.
2	5.5	0.292	0.092		11.4	0.703	0.444
3	2.4	0.262	0.137		12.0	0.713	0.505
4	1.6	1.083	0.135	Low sodium diet	14.7	2.850	0.090
5	3.0	1.452	0.028		20.9	3.850	0.053
6	6.0	1.206	0.015		12.4	2.603	0.026
7	7.9	1.662	0.018		17.3	3.470	0.029
8	5.4	0.525	0.025		16.3	1.520	0.076
9	1.9	0.220	0.115		10.4	0.759	0.510
10	3.1	0.206	0.145		11.9	0.762	0.536

(mean of 5 rats in each group)

Table 13 Alterations of potassium and sodium in urine of rats injected with 1cc of 4% formalin

Days	Fat diet group				Fat-free diet group		
	Urine volume	Potassium excretion	Sodium excretion		Urine volume	Potassium excretion	Sodium excretion
1	3.7 cc	0.308meq.	0.196meq.		6.8 cc	0.492meq.	0.408meq.
2	3.6	0.294	0.056	4% Formalin 1cc	13.4	0.632	0.160
3	2.1	0.376	0.026		7.7	0.398	0.136
4	2.0	0.312	0.206		8.8	0.650	0.362

(mean of 5 rats in each group)

5. Effect of a Single Injection of 1cc of 4% Formalin (Fig. 11 and Table 13)

After 1cc of 4% formalin was injected into the dorsal muscle, a marked increase of urine volume occurred in the fat-free diet group. After 24 hours the Na/K ratio fell and remained low for 48 hours, even lower in the fat diet group. By 72 hours it had returned to nearly normal. This low value was due mainly to the restriction of sodium excretion.

6. Effect of Repeated Daily In-

Fig. 11 Alterations of Na/K ratio in urine of rats injected with 1cc of 4% formalin

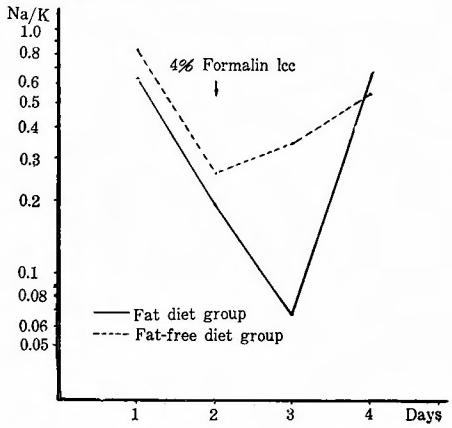
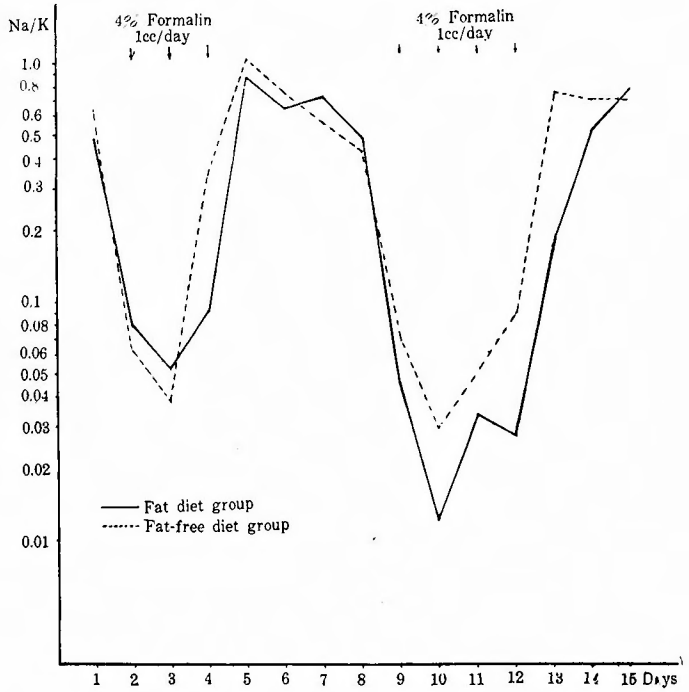


Table 14 Alterations of potassium and sodium in urine of rats in jected with 1cc of 4% formalin/day for 3-4 days

Days	Fat diet group				Fat-free diet group		
	Urine volume	Potassium excretion	Sodium excretion		Urine volume	Potassium excretion	Sodium excretion
1	1.5 cc	0.417meq.	0.200meq.		11.3 cc	0.995meq.	0.641meq.
2	15.1	0.684	0.054	4% Formalin 1cc/day	26.3	1.130	0.071
3	14.1	0.410	0.022		28.9	0.904	0.032
4	24.8	0.596	0.054		41.2	1.504	0.508
5	5.5	0.498	0.427		24.1	0.764	0.765
6	2.7	0.421	0.269		10.3	0.980	0.710
7	3.2	0.414	0.291		11.1	1.290	0.703
8	5.3	0.439	0.205		8.7	1.190	0.494
9	11.2	0.403	0.018	4% Formalin 1cc/day	21.9	1.160	0.068
10	13.2	0.416	0.005		22.0	1.070	0.031
11	12.8	0.620	0.021		18.7	1.210	–
12	18.8	0.528	0.014		24.1	1.000	0.089
13	6.6	0.615	0.110		8.7	0.888	0.735
14	5.2	0.376	0.190		9.0	1.070	0.733
15	4.2	0.345	0.262		8.8	1.010	0.704

(mean of 5 rats in each group)

Fig. 12 Alterations of Na/K ratio in urine of rats injected with 1cc of 4% formalin/day for 3~4 days



jections of 1cc of 4% Formalin (Fig. 12 and Table 14)

1cc of 4% formalin was injected daily for 3 days, and after a 4 day break, for 4 more days. The Na/K ratio of both groups fell, and the fat diet group showed an obvious increase of urine volume. The changes in the Na/K ratio both groups were similar throughout the experiment. The fall in the Na/K ratio was due to decreased sodium excretion. After 3 days of injections, the ratio was higher than before the injections and returned to normal after 1 or 2 days. During the second course of injections the results were the same. In TAMAKI's experiment on formaldehydogenic corticosteroid concentration in blood under the same conditions, there was also a definite difference between the reaction patterns of two groups.

C. Changes in Red Cell Count, Hematocrit and Mean Red Cell Volume by Large Intravenous Infusions of 5% Glucose (Fig. 13 and Fig. 14)

Rats of both groups were anaesthetized by injections of 4cc of 20% urethane solution per kg and then 70cc/kg of 5% glucose solution was injected slowly (5 to 10 minutes) into the jugular vein. Blood was withdrawn before the infusion and 30 minutes, one hour and 2 hours after (0.8cc at one time), and the red cell count, hematocrit and red cell volume were determined. The average weight of the rats was 267 g and the circulating blood volume was approximately 20cc. The 3.5cc blood removed for the studies must not be ignored, even though it was kept as little as possible. Before infusion the fat-free diet group had a high red cell count

and hematocrit value, indicating blood concentration, and the red cell volume was small, also. The serum potassium of both groups was nearly equal, but the serum sodium of the fat-free diet group was a little low, while the red cell sodium was high, and the red cell potassium was low, indicating that the concentration gradient

Fig. 13 Red cell count, hematocrit value and mean red cell volume when a large volume of 5% glucose solution was infused intravenously

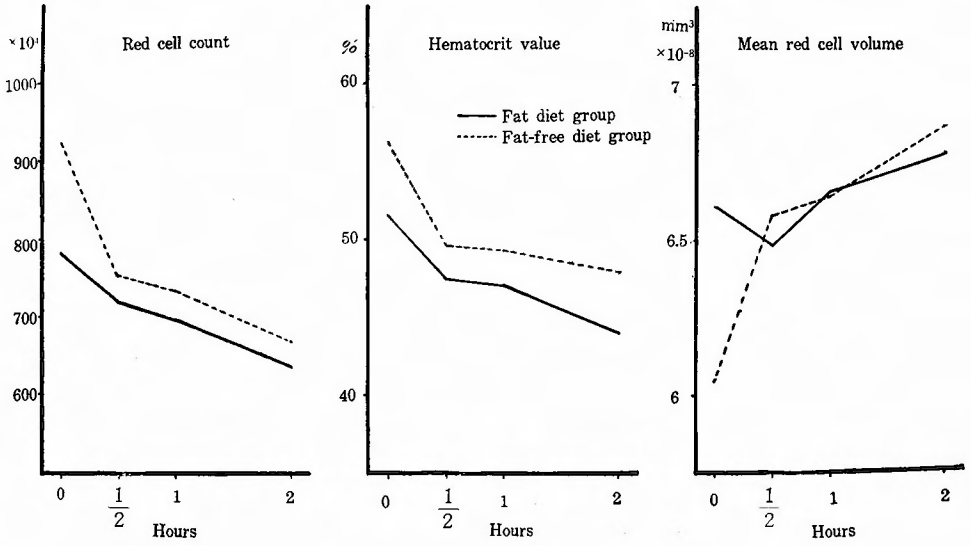
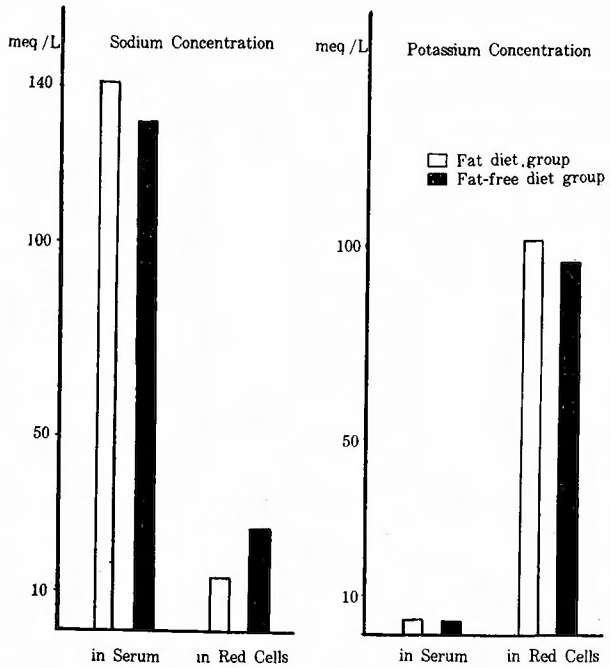


Fig. 14 Sodium and potassium concentration in serum and red cells



through the red cell membrane was small in the fat-free diet group. When a large volume of 5% glucose solution was infused intravenously, the red cell count and hematocrit suddenly decreased due to blood dilution, more so in the fat-free diet group, which suggests that the circulating blood volume may have been smaller before the infusion. The values in both groups 1 and 2 hours after the infusion were about the same. The red cell volume of the fat-free diet group increased suddenly 30 minutes after the infusion and then continued increasing gradually. That of the fat diet group, however, increased gradually without a sudden rise at 30 minutes. The increase of the red cell volume was probably due to the flow of water into the red cells. Therefore, the flow of water into the red cells was apparently swifter in the fat-free diet group than in the fat diet group.

Ⅳ. DISCUSSION

A. Potassium Balance

According to HOFFMAN[22] and GAMBLE[23], the intracellular and extracellular distribution of water and electrolytes of a healthy man is as seen in Table 15. As it points out clearly, the intracellular water accounts for nearly 50% of the body weight and contains more than 20 times the concentration and over 50 times the quantity of potassium as the extracellular fluid and 98% potassium, almost all of it in body, is almost limited to the intracellular space. On the other hand, the sodium is concentrated in the extracellular fluid. The reason for this phenomenon of limitation of electrolyte to inside or outside cells, has finally been explained by a new concept: the active transfer of electrolytes through the cell membrane. USSING[21] found that the protoplasm of the basal cell nearest the corium of the frog's skin had mechanism for actively transporting sodium inside and named this the "Sodium-pump", and he considered that potassium was passively transported in the opposite direction on account of the electric potential of the membrane caused by the active trasport. It has recently been generally admitted that this kind of mechanism or a similar type of active transfer can take place through the cell membrane of all living cells. In regard to the potassium balance: a healthy man is supposed to ingest 70 meq. to 100 meq. of potassium a day, 90% of which is excreted through the kidney (HOFFMAN[22]), a very small amount being excreted in the sweat and stools. Since the daily intake and output of potassium are more than the extracellular potassium, when the potassium balance becomes positive or negative, it is soon reflected in alterations of the intracellular potassium. As is

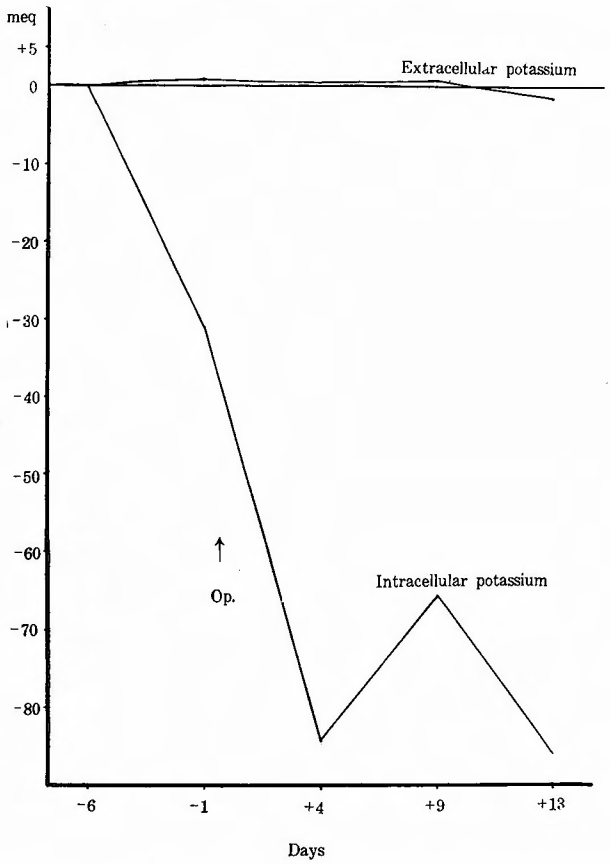
Table 15 The intracellular and extracellular distribution of water and electrolytes of a healthy man weighing 70 kg

	Extracellular space	Intracellular space
Water	14 *l*	35 *l*
Potassium concentration	5 meq./*l*	115 meq./*l*
Potassium	70 meq.	4025 meq.
Sodium concentration	140 meq./*l*	10～36 meq./*l*
Sodium	1960 meq.	350～1260 meq.

(by Hoffman, W. S. and Gamble, J. L.)

indicated by the changes in extracellular and intracellular potassium in the experimental dog on the 6 and one days before and 4, 9 and 13 days after operation (Fig. 15), the negative potassium balance after the operation is due to loss of intracellular potassium. That is, when the potassium intake is low or nil, almost all of the potassium excreted in the urine is intracellular potassium.

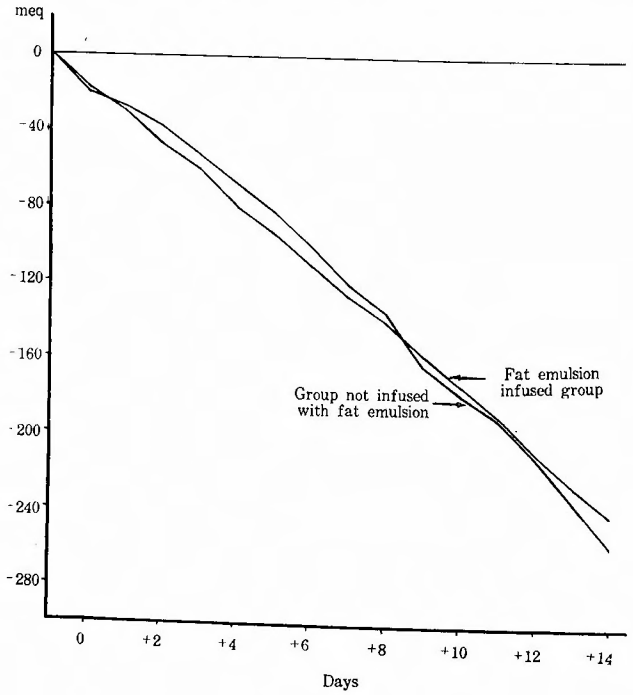
Fig. 15 Changes of intracellular and extracellular potassium in the dog before and after operation



The kidney has the ability to retain sodium, but not potassium (EVANS[25]). It is pointed out that the potassium concentration in the urine of a healthy man is 4 to 12 times the concentration in the plasma (20 to 60 meq./*l*) and the potassium lost in the urine is 40 to 50 meq. a day even during fasting or on a potassium-free diet (TARAIL[23]). This is because the reabsorption rate of potassium in the urinary tubules is 93.4% whereas that of water and sodium is 99.5% (GAMBLE[23]). The potassium metabolism of gastrectomized dogs fed a low potassium diet is explained by the destruction of tissue protein resulting from the stress response to the operation, the subsequent discharge of potassium out of the cells, and the increased potassium excretion in the urine. However, if blood sugar is removed to form glycogen, the process involves the step K-glucose-6•phosphate; therefore some

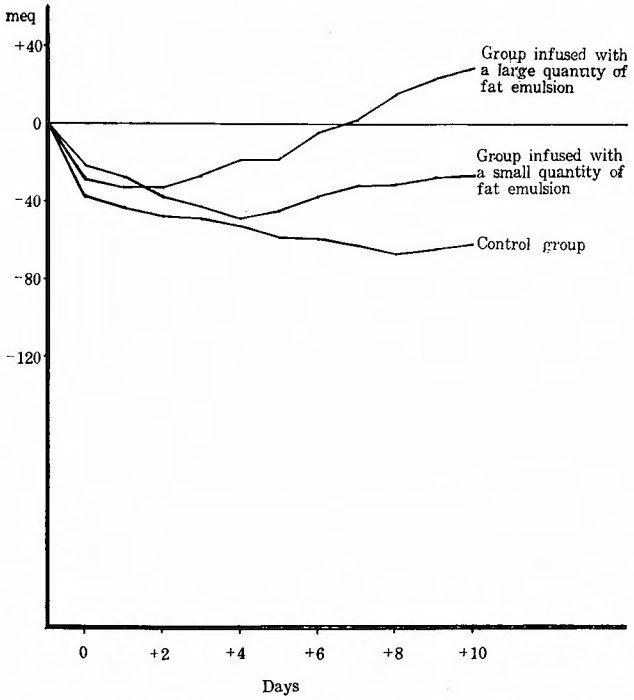
potassium enters the cells in this way, and then some of it is discharged into the extracellular space when the glycogen is redissolved (FENN[27]). It has also been proved that 3 meq. of potassium per g of nitrogen is taken into cell space when new tissue is built by the increase of protein (ELKINTON[28]). Thus, potassium is closely connected with the metabolism of carbohydrate and protein and their transport through the cell membrane. And in addition to this anabolism and catabolism, it is able to move with the increase and decrease of extracellular ion concentration. For instance, the K/N ratio became more than 3.0 for several days after the operation, and less than 3.0 if excess potassium was taken as sodium was restricted. Consequently, the negative potassium balance of the gastrectomized dog fed a low potassium diet is caused not only by potassium loss to the extracellular space due to destruction of tissue protein after the operation, but also to the active transfer of potassium from the cells to the extracellular space while, at the same time, the extracellular potassium concentration decreases because of the low potassium intake. During this potassium deficient phase, the anabolism of tissue protein is more and more imperfect because of the calorie deficit[29][30], and although the protein sparing action reported by HANAFUSA[4] should be brought about by injections of fat emulsion, the loss of intracellular potassium increases almost lineary in both groups when the supply of calories and potassium is as low as this (Fig. 16), for the potassium sparing action of the fat emulsion is hidden by the amount of potassium loss due to the deficit of extracellular potassium so no definite difference between the two groups can be seen. After all, these conditions cause a too extreme potassium

Fig. 16 Loss of intracellular potassium in dog fed a low potassium diet



insufficiency for the infusion of fat emulsion to have any beneficial effect. When a high potassium diet was given, gastrectomy was safe as far as potassium balance was concerned. Only the outflow of intracellular potassium due to the deficit of extracellular potassium is completely prevented in this case, so if tissue protein destruction can be reduced by the infusion of a little fat emulsion, the outflow of intracellular potassium is also mitigated as much as possible, so the fat-emulsion-infused group loses much less potassium than the control group, as Fig. 17 shows. And there is even evidence of the inflow of potassium into the cells in the fat-

Fig. 17 Loss of intracellular potassium in dog fed a high potassium diet



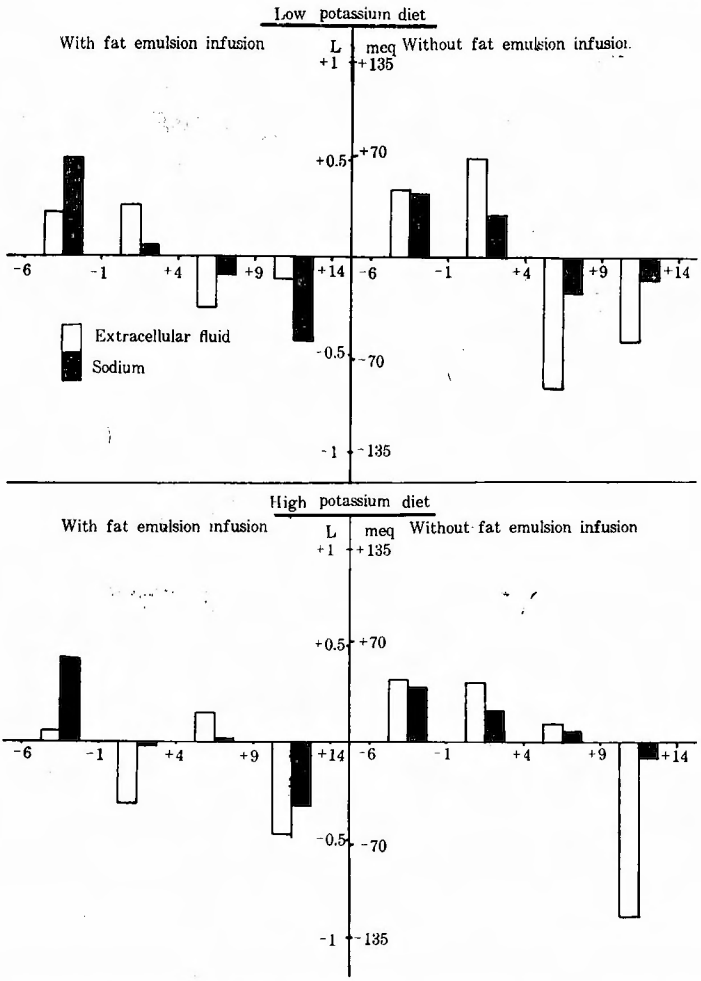
emulsion-infused group on the 5th day after operation, when the restoration of tissue begins. The effect of the fat emulsion is definite, and the weight curve bears this out. One of the reasons why the outflow of intracellular potassium is thus arrested by the infusion of fat emulsion is certainly that the fat emulsion reduces tissue protein destruction in response to stress. And yet, the calorie gain from the fat emulsion supplied in this experiment is too small for this to be the whole explanation. EFA are fully supplied by infusion of this fat emulsion before operation, so that their various characteristic action[31] can function smoothly to spare carbohydrate and avoid as much as possible the consumption of dépot-glycogen. Therefore, it is thought that these factors also contribute to preventing the outflow of intracellular potassium after operation. Moreover, the structural unit of tissue cells is today thought to be lipoprotein, not protein alone, so it goes without saying that the infusion of a fat emulsion containing all the EFA before and after the operative stress acts more effectively in the restoration of cells and their functional recovery.

These specific characteristics of the fat emulsion work together to arrest the outflow of intracellular potassium. These facts were further clarified by the experiment of infusing a large quantity of fat emulsion in which the loss of potassium after operation was very greatly reduced, the potassium balance became positive very early, and the anabolism of tissue protein began smoothly and early. Furthermore, repeated infusions of 4cc per kg (0.8g per kg) caused no abnormality of fat metabolism.

B. Sodium Balance

Most of the sodium, as has been previously mentioned, is in the extracellular space, 350 to 1,260 meq. being intracellular and 2,000 meq. extracellular. But it is not so definitely localized as potassium. As long as the extracellular electrolyte concentration is stable, the quantitative exchange of sodium in and out of the body is closely connected with alterations of extracellular fluid volume in contradistinction to the case of potassium, so it must be taken into consideration. It is admitted by many investigators that sodium, in small amounts, moves into the cells as potassium moves out. But when the exchange of intracellular and extracellular sodium was calculated in the same way as the potassium changes had been determined, it came out that the quantity exchanged surpassed even the total intracellular sodium of a dog weighing 10kg. Such a contradiction can be thought to be due to the following reasons: (1) Intracellular sodium is not measured directly, but extracellular sodium and total sodium are measured and difference calculated. However, since extracellular sodium is several times more than intracellular, the errors of the former very greatly influence the calculation of the latter. (2) Some of the sodium-rhodanate used in measuring extracellular fluid volume enters the cells so that the calculated rhodan-space is greater than the actual extracellular fluid volume. Therefore, the intracellular sodium concentration cannot be determined as a fixed value. Consequently, the exchange between intracellular and extracellular sodium cannot be discussed quantitatively on the basis of this experiment alone. And yet, as it is almost possible to presume from the localization of sodium that even if the movement of sodium into the cells cannot be ignored, it is slight when compared with its variation with changes in the extracellular fluid volume, the sodium balance can be regarded as varying with the extracellular fluid volume with only a slight observed error. When the extracellular fluid volume is compared with the sodium balance measured on the same day, the two columns placed next to each other in the diagram (Fig. 18) would be expected to come to the same height. However, their height are different because of the error due to the movement of sodium into the cells and to the difference between the rhodan-space and the real extracellular fluid volume. Nevertheless, despite the difference in the height of the columns water and sodium have a general tendency to parallel each other, and the sodium balance can be considered to show alterations of the extracellular fluid volume. The fact that the extracellular fluid volume changed less indicates that the sodium balance after the operation varied less in the fat-emulsion-infused group than in the control group. This is in agreement with the results of TAMAKI's[9] and KOBAYASHI's[7]

Fig. 18 Extracellular fluid volume compared to sodium balance



studies. The changes in sodium after the operation were further decreased by high potassium intake, indicating that potassium deficiency influences sodium metabolism considerably, too.

SELYE has described a series of non-specific reactions to stress, the General Adaptation Syndrome, in which the main factor is the hypothalamo-pituitary-adrenal system, and ACTH and glucocorticoid are the adaptation hormones. The physiological changes which take place during surgical convalescence described by MOORE[12] are thought to be of the same nature. According to their opinions, almost all of the sodium is kept in the body with only a very small amount being excreted right after the opertion. The secretion of glucocorticoid begins a few hours after the operation is started and that of mineralocorticoid increases a few days later. The moment the operation starts and throughout its duration, the secretion of ADH increases and is believed to play the most important role in water retention. But the sodium balance on the day of operation was negative in both low and high potassium diet groups, because water intake was decreased to about 1/3 of that on

the day before operation and sodium intake to about 1/2; therefore the water balance turns negative despite the action of ADH and the extracellular fluid volume is decreased temporarily. When the water intake was made almost equal to that before the operation by increasing the amount of fluid infused on the day of operation and the lst and 2nd after in the experimental infusion of large amount of fat emulsion, the sodium balance became positive. LLAURADO[33)~38)] and IMAO[33)~41)] have recently drawn attention to aldosterone as a mineralocorticoid which increases in the urine by 24 hours after the operation and returns to its preoperative value after about one week. Therefore, the theory that sodium retention on the 2nd and 3rd day after stress is controlled by glucocorticoid plus factors other than the adrenal cortex (reduced renal hemodynamics due to increased adrenalin, increased ADH secretion, acceleration of PITTS' mechanism and reduction of circulating plasma volume) must be re-examined taking into account the alterations of aldosterone concentration in blood and urine.

C. Changes in Na/K Ratio in Urine and the Secretion of Aldosterone

In 1953 SIMPSON and TAIT[42)~44)] extracted from the amorphous fraction of the adrenal cortex a new corticosteroid with a strong sodium retaining action and named it electrocortin. WETTSTEIN and REICHSTEIN[15)46)] next succeeded in crystallizing it and named it aldosterone. Since then it has received wide attention as one of the mineralocorticoids secreted physiologically by the adrenal cortex. SIMPSON stated that it has 25 times the sodium retaining effect of DOCA, 5 times the potassium excreting effect and nearly 100 times the Na/K ratio diminishing effect. It is also said to be 25 to 30 times as effective in maintaining the life of adrenectomized dogs and 3 times as stable to cold as cortisone[47)~51)]. About 200γ of aldosterone is secreted in adults each day, but only 1 to 6γ is excreted in the urine (VENNING[52)53)]). The ratio between secretion and excretion is not constant. Especially when the inactivation of aldosterone by the liver is interfered with, it becomes even more irregular (KUMAGAYA[54)]).

As there is a correlation between the Na/K ratio in the urine and the aldosterone concentration in the suprarenal venous blood, i. e. aldosterone secretion, it is believed best to use the Na/K ratio (or K/Na ratio) in the urine as an index in the bioassay of aldosterone. If the logarithm of the Na/K ratio is used, a linear correlation can be obtained[34)]. Experiment (B) was undertaken with the view that the aldosterone activity in the body could be indirectly determined with a certain degree of quantitative accuracy by measuring the Na/K ratio in the urine. Although there are different opinions about the region that secretes aldosterone and the mechanism regulating it, the following theory has general support. Unlike hydroxycorticoid and ketocorticoid, aldosterone is secreted by the glomerular zone of the adrenal cortex. Although glucocorticoid secretion is increased by repeated large injections of ACTH, the secretion of aldosterone shows only a slight temporary increase, and then it decreases to the preinjection level or lower. The Na/K ratio did not fall even with injections of 1mg of ACTH-Z once or 4mg daily for 2 days; on the contrary, it even started to increase. This means that the secretion of

aldosterone is not influenced by ACTH in either dosage schedule. Glucocorticoid has been said by SWINGLE[55], KUMAGAYA[54] and CÁMARA[53] to be an anti-aldosterone steroid, and if it is injected together with aldosterone, to be antagonistic and lessen its effect[57]. It is accordingly believed that the secretion of glucocorticoid is promoted by injections of large amount of ACTH-Z, which thus diminish the action of aldosterone and increase Na/K ratio. Then what controls the secretion of aldosterone, since ACTH is not the main factor? Many investigators believe that body fluid volume does. Restriction of sodium intake and loading with potassium are considered to stimulate the secretion of aldosterone; yet they do not do this by altering the potassium and sodium concentration in serum or the total amount of potassium and sodium in the body but by causing changes in extracellular fluid volume. FARRELL[58][59] believes that there is an aldosterone regulating center in the diencephalon which receives stimuli from peripheral receptors sensitive to changes in electrolyte concentration and which secretes glomerulotropic hormone (G. T. H.). This hormone reaches the glomerular zone of the adrenal cortex humorally as does ACTH and stimulates aldosterone secretion. In the experiment with a low sodium diet, a conspicuous fall of the urinary Na/K ratio occurred as soon as the diet was started, and sodium was effectively retained. This indicates that fat and fat-free diet groups could endure the low sodium diet by a full secretion of aldosterone. The fact that the Na/K ratio was still low on the lst day when the standard diet was resumed, shows that the ability to secrete aldosterone is prolonged beyond the immediate necessity. In this experiment no difference was seen between the rats in the fat diet group and those in the fat-free diet group as to Na/K ratio changes. Stress caused by the injection of formalin also causes the Na/K ratio to decrease definitely. As has been proved by TAMAKI's[71] experiment, formalin also works well as stressor for glucocorticoid and has been used widely in experiments on stress response since SELYE's first report on this subject. Formalin has this action even though starvation was not capable of causing an increased secretion of aldosterone. These findings show that both starvation and the injection of formalin non-specifically effect glucocorticoid secretion as stressors but that formalin only is specific for aldosterone. For instance, the appearance of many vacuoles in the glomerular zone following injections of formalin (MORI[70]) suggests that it acts directly on the glomerular zone and indirectly on the fascicular zone through the medium of ACTH. TAMAKI admitted the distinct difference in the concentration of formaldehydogenic corticosteroid in blood between the rats on the fat diet group and those of the fat-free diet group caused by injections of formalin, but in both groups the Na/K ratio fell in about the same degree and no definite difference was recognized in any of these stress experiments.

As noted above, there was no difference in the changes in the urinary Na/K ratio between the fat diet and fat-free diet group; this was to be expected in the experiments with ACTH and with fasting, that did not cause increased secretion of aldosterone, but it was also true in the experiments with low sodium diets and repeated injections of formalin, that are known to cause the secretion of aldosterone

to increase. These facts indicate that adrenocortical capacity is not decreased by EFA insufficiency at least as far as mineralocorticoid is concerned. Previous reports from our laboratory have indicated that the ability to secrete glucocorticoid is distinctly decreased in organisms lacking EFA, and that so-called relative hypoadrenocorticism occurs because the adrenal cortex is not able to provide the quantity of glucocorticoid that the organism needs to meet the stress[5][8][21]. This theory is applicable only for glucocorticoids in relation to this experiment, and not to mineralocorticoids at all. MATSUDA[5] has investigated the histological and histochemical manifestations of adrenocortical response in the starvation test in the two groups of rats (low fat diet and high fat diet). Although he noted such exhaustive changes as the depletion of lipid granules in the adrenal cortex, bleeding and cytolysis in the low fat diet group, none of these changes were seen in the high fat diet group. It is noteworthy that these changes were not seen in the glomerular zone but were limited to the fasticular zone; no difference was seen in the glomerular zone between the two groups. This finding is in perfect agreement with the results of this experiment. Thus there seems so far to be no indication of a direct cause and effect relationship between EFA deficiency in the body and the biosynthesis of mineralocorticoid. This problem must still be brought to its final conclusion by experimental biosynthesis of aldosterone with isotope C^{14}. Furthermore, as some other unknown factors besides EFA may be involved in the process of aldosterone biosynthesis, the writer's experiment might led to the same results even without any direct causal relationship. As has already been mentioned, though, dehydration or excessive fluid supply is frequently present during operative stress, at which time the permeability of capillary walls or cell membranes to water is greatly increased in organism lacking EFA, which are directly involved in the construction of capillary walls or cell membranes; therefore, slight dehydration or overhydration causes unexpectedly great changes of water distribution in the body. There is clear evidence that the change of extracellular space at that time acts as a stressor and the secretion of aldosterone is easily influenced excessively by slight dehydration or overhydration. Even if EFA had no direct connection with aldosterone biosynthesis, they would increase or suppress the secretion of aldosterone easily secondarily; and these changes would be very great in organisms lacking EFA. This is probably one of the main reasons that the movement of electrolytes was greatly reduced in dogs given fat emulsion before and after gastrectomy as compared with the control group. Therefore, it is reasonable to think that fat supply also has a great influence on the secretion of aldosterone, even though secondarily. Next, a very simple experiment was done to investigate how the lack of EFA changes the permeability of cell membranes to water as expected.

D. Changes of Water in Red Cells

PANOS[11] has reported that one of the most striking characteristics of fat deficiency was elevation of the basal metabolic rate. In consequence, the basal oxygen consumption of rats fed a fat-free diet increases, while their water consumption is twice that of the control group, and the increase in weight of the fat-free diet

group is only 67% of the fat diet group although they receive the same number of calories. The insensible water loss of the fat-free diet group was up to double that of the high fat diet group at 40% humidity. These findings point out that the permeability of skin to water is abnormally accelerated, and it is not hard to imagine that the body water of animals lacking fat is lower than in those supplied with enough fat. TAMAKI[7] has reported that the combined use of the emulsion and RINGER's solution before gastrectomy is very helpful in maintaining circulating blood volume and extracellular fluid volume at nearly normal levels, while this was not possible when fat emulsion was not used. KOBAYASHI[7] obtained the same results in his experimental studies on dogs.

The writer also could confirm the increase of water consumption and the decrease of body water reported by PANOS, from the large urine volume in the fat-free diet group in Experiment (B), the great increase in the red cell count and hematocrit value, the small mean red cell volume and the hasty fall of the red cell count and hematocrit value after the infusion of a large quantity of 5% glucose solution in Experiment (C). EFA form a part of certain lipoproteins, which are a combination of lipids and proteins, and indispensable structural units of tissue. Recently, the importance of the structural function of EFA has attracted attention (SINCLAIR[9]); the structural deficiency of cell membranes caused by EFA insufficiency results in increased permeability, and NAGASE[8] has investigated this as one of the factors in postoperative pulmonary edema. Moreover, it is now generally believed that active transport through the cell membrane occurs with carrier which requires energy consumption. In 1956 SOLOMON[12] discovered in red cell membranes a sort of fat that has affinity for cations, especially the potassium ion, and reported that it was soluble in lipids and might be the carrier of electrolytes through the cell membrane. These findings suggest that EFA may have a more important function in cell membrane permeability by participating directly in the transport of cations in addition to their importance as part of a structural unit of cell membranes. Therefore, it is considered that the mechanism keeping the gradient of ion concentration inside and outside of the cell depends on the structure of the cell membrane plus the carrier and the energy system making the carrier work, and that when this mechanism is damaged in EFA deficiency changes in the permeability of cell membranes result. The low gradient of sodium and potassium concentration in Experiment (C) seems to support this concept. The fact that the mean red cell volume of the fat-free diet group is more rapidly increased by the injection of 5% glucose solution than that of the high fat diet group indicates the ease and rapidity with which water passes into cells, proving that the permeability of cell membranes is much greater in the former than in the latter.

V. CONCLUSION

The following conclusions were reached about the relations between fat and electrolyte metabolism and the function of mineralocorticoids in a series of experi-

ments on dogs infused repeatedly with 20% sesame oil emulsion and rats fed fat-free diets.

1. Repeated supplies of fat do not disturb the stability of sodium and potassium concentrations in serum at all.

2. The combined use of enough potassium and fat is effective in preventing potassium loss after operation and in providing a definite protein sparing action.

3. A double dose of fat further improves the potassium balance.

4. The fat supply is able to maintain sodium balance so that it alters minimally with body fluid changes in the pre- and postoperative stages and stays close to normal throughout.

5. The secretion of mineralocorticoid is accelerated by neither the injection of ACTH nor fasting, but it is definitely stimulated by a low sodium diet and the injection of formalin.

6. In this experiment, a direct cause and effect relation between EFA and mineralocorticoid was less evident than between EFA and glucocorticoid. Mineralocorticoid still possessed fully its reserve secretory capacity even when EFA were deficient. However, the final decision as to whether or not EFA are involved in the biosynthesis of mineralocorticoids must be left to future experiments.

7. A decrease of body water and an increase of red cell membrane permeability are noted in EFA deficiency, which damage the mechanism maintaining the gradient of ion concentration on either side of the cell membrane and thus change the permeability of cell membranes to water and electrolytes.

8. Therefore, although this experiment could not prove a direct relationship between EFA and the biosynthesis of mineralocorticoid, the unexpectedly great changes in the extracellular space which develop easily in EFA deficiency when dehydration and overhydration are induced, as at times of operative stress, can be explained by increase in permeability of capillary walls and cell membranes. This changes in the extracellular space act as a stressor and has a great influence on the secretion of aldosterone. For this reason the group infused with fat emulsion before and after operation had much less change in electrolyte balance than that not receiving fat emulsion. Therefore, the use of fat emulsion infusions is considered to be a large factor in keeping the electrolyte distribution in the body consistently close to normal.

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REFERENCES

1) Tsukada, A.: Studies on the intravenous administration of the fat emulsion in the light of protein metabolism. Arch. jap. Chir., 23, 215, 1954.
2) Osa, H.. Experimental studies on the intravenous administration of fat emulsion. Ibid., 25. 154, 1956.
3) Kuyama, T.: Clinical studies on the nutritional effects of intravenous administration of fat emulsion. Ibid., 27, 64, 1958.
4) Hanafusa, S.: Clinical studies on the nutritional effects of fat emulsion administrated intra-

venously and by nasal tube feeding. Ibid., **28**, 1356, 1959.
5) Matsuda, S.: Experimental studies on the nutritional significance of fat from the view point of its effects on the liver glycogen content. Ibid., **28**, 3008, 1959.
6) Tamaki, A.: Influence of intravenous infusion of sesame oil emulsion on fluid distribution. Ibid., **28**, 3028, 1959.
7) Kobayashi, M.: unpublished.
8) Nagase, M.: Experimental study on pathogenesis of acute postoperative pulmonary edema. Arch. jap. Chir., **29**, 67, 1960.
9) Sinclair, H. M.: Effect of deficiency of essential fatty acids. I. Deficiency of essential fatty acids in lower animals. Essential Fatty Acids, p. 249, Butterworths Scientific Publications, 1958.
10) Saito, M.: Chemical examinations with spectrophotometer in clinic. p. 299, Nanzando, 1952.
11) Hukushima, S.: Flame photometry (Review). Kagaku no Ryōiki, **11**, 669, 1957.
12) Ishida, R.: Flame photometry (I). Ibid., **8**, 163, 1954.
13) Ishida, R.: Flame photometry (II). Ibid., **8**, 239, 1954.
14) Oyagi, Y.: A present aspect of flame spectrophotometry (Enkōbunkōbunseki no Genkyō). Bunseki Kagaku, **4**, 179, 1955.
15) Onzai, K. et al.: Measuring errors of flame photometry (Enkō-kōdokei ni yoru Teiryō-bunseki no Gosa ni tsuite). Ibid., **4**, 188, 1955.
16) Hukushima, S.: A microanalysis of sodium in lead by flame photometry (Enkō-kōdohō ni yoru Namari-zikin tyū no Biryō-natrium no Zinsokuteiryō-hō). Ibid., **5**, 704, 1956.
17) Kuehns, K. und Mueller, G.: Ergebnisse und Fehlerquellen flammenphotometrischer K- und Na-Analysen in Serum und Organen mit einer modifizierten Apparatur von B. Lange. Z. physiol. Chem., **294**, 86, 1953.
18) Huzii, Y.: Biochemical experimental methods—Quantitative analysis (Seikagaku Zikken-hō—Teiryō-hen). p. 19, Nanzandō, 1958.
19) Hinohara, S.: Water and electrolyte in clinical medicine. p. 79 and p. 87, Igakusyoin, 1957.
20) Hayashida, T.: Preoperative treatments (Syuzyutsu Zensyochi). Nihon-geka-zensyo Vol. **5**, p. 26, Nihon-geka-zensyo-kankōkai, 1957.
21) Tamaki, M.: unpublished.
22) Hoffman, W. S.: Clinical physiology of potassium. J. A. M. A., **144**, 1157, 1950.
23) Gamble, J. L.: Chemical anatomy, physiology and pathology of extracellular fluid. Harvard univ. press, 1959.
24) Ussing, H. H. et al.: Active transport of sodium as the source of electric current in the short-circuited isolated frog skin. Acta Physiol. Scand., **23**, 110, 1951.
25) Evans, E. I.: Potassium deficiency in surgical patients. Ann. Surg., **131**, 945, 1950.
26) Tarail, R. and Elkinton, J. R.: Potassium deficiency and the role of the kidney in its production. J. Clin. Invest., **28**, 99, 1949.
27) Fenn, W. O.: The role of potassium in physiological processes. Physiol. Rev., **20**, 377, 1940.
28) Elkinton, J. R. et al.: Inactive cell base and the measurement of changes in cell water. Yale J. Biol. and Med., **17**, 383, 1944.
29) Suzuki, I. et al.: Influence of potassium on nitrogen balance in surgical undernutrition. J. Jap. Surg. Society, **56**, 784, 1955.
30) Beal, J. M. et al.: The influence of calorie and potassium intake on nitrogen retention in man. Ann. Surg., **138**, 842, 1953.
31) Hikasa, Y. et al.: Fat metabolism and its nutritional significance, studied with fat emulsion (Shishitsu-nyūzai o motte suru Shishitsu-taisya narabi ni Eiyōgakuteki Igi ni tsuite no Kenkyū). Saishin igaku, **13**, 2954, 1958.
32) Moore, F. D.: Bodily changes in surgical convalescence—1. The normal sequence—Observations and interpretations. Ann. Surg., **137**, 289, 1953.
33) Llaurado, J. G.: Sodium-potassium ratio and excretion of aldosterone in urine of patients following surgical trauma. Proc. Univ. Otago med. sch., **32**, 20, 1954.
34) Llaurado, J. G.: Further studies on the excretion of aldosterone following surgical trauma; Transient aldosteronism. Ibid., **33**, 19, 1955.

35) Wettstein, A., Neher, R. and Llaurado, J. G.: Further studies on postoperative transient aldosteronism; Chemical identification of aldosterone. Ibid., **34**, 7, 1956.
36) Llaurado, J. G.: Early changes in water, sodium, potassium and aldosterone excretion after hypophysectomy in man. Ibid., **35**, 18, 1957.
37) Llaurado, J. G. and Woodruff, M. F. A.: The stimulus to postoperative transient aldosteronism. Ibid., **35**, 19, 1957.
38) Llaurado, J. G. and Pearse, V. T.: On the electrolyte response after bilateral adrenalectomy. Ibid., **35**, 21, 1957.
39) Imao, B.: Urinary excretion of aldoserone following surgery. Clin. Endoclin., **6**, 729, 1958.
40) Imao, B. et al.: Water and elecrolyte balance following surgery, Report I. (Some observations on basic experiments by photoelectric spectrophotometer and clinical results). J. Jap. Surg. Society. **59**, 784, 1958.
41) Imao, B.. Postoperative treatment, especially fluid transfusion, and aldosterone (Zyutsugosyochi tokuni Hoeki to aldosterone). Sinryō, **12**, 1634, 1959.
42) Tait, J. F. and Simpson, S. A.: The effect of adrenal extract on mineral metabolism. Lancet, **262**, (I), 122, 1952.
43) Tait, J. F. and Simpson, S. A.: Secretion of a salt-retaining hormone by the mammalian adrenal cortex. Ibid., **263**, (II), 226. 1952.
44) Tait, J. F., Simpson, S. A. and Gundy, H. M.: A new adrenal hormone. Ibid., **265**, (II), 551, 1953.
45) Simpson, S. A., Tait, J. F., Wettstein, A., Neher, R., Euw, J. V. und Reichstein, T.: Isolierung eines neuen kristallisierten Hormons aus Nebennieren mit besonders hoher Wirksamkeit auf dem Mineralstoffwechsel. Experimentia, **9**, 333, 1953.
46) Simpson, S. A., Tait, J. F., Wettstein, A., Neher, R., Euw, J. V., Schindler, O. and Reichstein, T.: Konstitution des Aldosterone, des neuen Mineralocorticoids. Ibid., **10**, 132, 1954.
47) Oshima, K.: Aldosterone and its clinical significance (Aldosterone no Tenbō to Rinsyō). Saishinigaku, **13**, 1701, 1958.
48) Oshima, K.: Relationship between aldosterone and metabolism of body fluid and electrolyte. Clin. Endoclin., **6**, 684, 1958.
49) Torikai, T.: Primary aldosteronism. Ibid., **6**, 692, 1958.
50) Donomae, I.: Secondary aldosteronism. Ibid., **6**, 704, 1958.
51) Yoshitoshi, K.: Adrenal cortex and water- and electrolyte-metabolism (Hukuzin to Mizudenkaishitsu Taisha). Nihon-rinsyō, **14**, 276, 1956.
52) Venning, E. H.: Excretion of sodium-retaining substances. J. Clin. Endoclin., **14**, 784, 1954.
53) Venning, E. H.. Studies on the excretion of the sodium-retaining corticoid. Ibid., **15**, 853, 1955.
54) Kumagaya, R.: Aldosterone and heart diseases (Aldosterone to Shin-sikkan). Sinryō. **12**, 1661, 1959.
55) Swingle, W. W. et al: Role of gluco- and mineralocorticoids in salt and water metabolism of adrenalectomized dogs. Am. J. Physiol., **196**, 283, 1959.
56) Cámara, A. A. and Schemm, F. R.: Corticotropin (ACTH) in heart disease: its paradoxical effect on sodium excretion in resistant congestive failure. Circulation, **11**, 702, 1955.
57) Abe, H. et al.: Anti-aldosterone substance (Kō-aldosterone Bussitsu, sono Sayō to Rinsyō). Sinryō, **12**, 1620, 1959.
58) Kimura, T.: Regulation of aldosterone secretion (Aldosterone no Bunpitsu no Tyōsetsu). Sinryō, **12**, 340, 1959.
59) Farrell, G.: Regulation of aldosterone secretion. Physiol. Rev., **38**, 709, 1958.
60) Mori, S. et al.: Histological manifestations of adrenocortical function (Hukuzin-hishitsu sono Kinō no Keitaigakuteki-hyōgen). Nihon-rinsyō, **14**, 306, 1956.
61) Panos, T. G. et al.: Metabolic studies in fat deficiency. Essential Fatty Acids, p. 205, Butterworths Scientific Publications, 1958.
62) Solomon, A. K. et al.: Possible cation-carrier substances in blood. Nature, **178**, 582, 1956.

和文抄録

脂質補給と電解質動態

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脂質補給が術前・術後を通じて水分代謝に極めて有効的である事実から，電解質代謝にもまた重要な役割を有するであろうことは，容易に考えられるところであるが，また更に脂質補給は体内コレステロールの代謝を介して電解質ホルモンの生合成にも，何らかの役割を演じていることも考えられるのである．

即ち以上の観点に立つて，20%ゴマ油乳剤を連続注入した犬および無脂質食を以て飼育したラッテを用いて一連の実験を行ない，その成績から，脂質補給と電解質動態との関係，更にこれを支配する電解質ホルモンとの関係を究明して次のような成績を得た．

(1) 脂質の連続投与は血清ナトリウム，カリウム濃度の恒常性を何ら攪乱するものではない．

(2) 充分なカリウムと共に，脂質を投与することは，手術後のカリウムの体外喪失を防ぎ，同時に著明な蛋白節約作用を招来せしめる．

(3) 脂質の投与量が増大すればするほど，カリウム平衡は更に一層改善される．

(4) 手術前後の体液量の変動に伴つて，著しく動揺するナトリウム平衡は，脂質の投与によつて最小限にとどめられ，正常状態に近い状態を終始保つことが出来る．

(5) 体内電解質ホルモンはACTH投与，絶食等によつてはその分泌亢進を来さないが，ナトリウム制限食およびフォルマリン注射によつて，その分泌は著明に亢進する．

(6) 本実験法のみをもつてすれば，不可欠脂酸と電解質ホルモンとの直接的因果関係は，不可欠脂酸と糖質ホルモンとの関係ほど密接なものではなく，不可欠脂酸の欠乏した状態下でも，なお電解質ホルモンはその分泌予備力を充分に有している．併し不可欠脂酸が電解質ホルモンの生合成に関与しているかどうかの最終的結論は今後の研究にまたなければならない．

(7) 不可欠脂酸の欠乏した個体では，体内水分量が減少し，赤血球膜の透過性が亢進することが認められる．而も不可欠脂酸の欠乏した状態下では，その結果細胞膜の内外イオン濃度の勾配を維持する作用にも障碍を惹起するようになり，水分および電解質の細胞膜透過性に変調を来たす．

(8) 従つて本実験では，不可欠脂酸と電解質ホルモン生合成との間に，直接的因果関係を立証することは出来なかつたが，不可欠脂酸の欠乏の有無は個体の毛細血管壁，および細胞膜の透過性の亢進と密接な関係を有するから，実際の手術侵襲時のように，脱水あるいは給水という条件が加わると，不可欠脂酸の欠乏した個体にあつては，意外に強く且つ容易に細胞外液相の変動を招き，それが Stressor として作用し，分泌されるアルドステロンの分泌状態にも著しい影響をおよぼす結果となる．このような意味でも，脂質の補給が術前・術後に亘り応用された際には，脂質が投与されなかつたものに較べて，電解質の変動が極めて少なく，従つてその生体内分布が終始殆んど正常状態近く保持される一つの大きな原因となり得る．